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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,451	12/22/2000	Xiaodong Wang	UTSD:546USD1	4000

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/11/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/748,451	WANG ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91 and 93-124* is/are pending in the application.

4a) Of the above claim(s) *91,93-110 and 117-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Rescission of Rejections Made in Prior Office Action

Applicant's election without traverse of the subject matter of Group IV, renumbered claims 111-116, in Paper No. 8 filed March 18, 2003, was acknowledged in Paper No. 9 mailed June 3, 2003. Examination of the subject matter of Group IV stated in the restriction requirement, Paper No. 6 mailed August 27, 2002, had been directed in Paper No. 9 to nucleic acid sequences encoding generic DNA fragmentation factor polypeptides of claims 111-115 and the specific DFF40 DNA fragmentation factor of claim 116. Claims 91, 93-110 and 117-126 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Paper No. 9 supplies for the record a copy of Applicant's PTO Form 1449 submitted with the Information Disclosure Statement, Paper No. 4 filed June 13, 2001, and executed by the Examiner, making of record the references considered in the present application as well as the parent application serial No. 09/061,702. Paper No. 9 also supplies for the record the PTO-Form 892 whereby the examiner made of record the published International Application of Halenbeck et al., WO 99/10501, which is not prior art but was pertinent to the disclosure of the instant application. Paper No. 9 had not acknowledged Applicant's claim to priority to the filing date of the parent application serial No. 09/061,702, which claim is acknowledged herein. In telephonic discussions of August 29 and September 5, 2003, between the examiner and Applicant's counsel it was agreed that Applicant should have received an examination of the invention of Group IV as claims drawn to polypeptides related to a disclosed DFF40 DNA fragmentation factor, rather than an examination of polynucleotides set forth in Paper No. 9. Consequently all rejections of record stated in Paper No. 9 are hereby RESCINDED and the following rejections are made of Applicant's desired subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 111-115 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 111-115 describe genera of polypeptides related to a disclosed human DFF40 DNA fragmentation factor having the amino acid sequence set forth in SEQ ID NO:2 by the recited inclusion of randomly-chosen arrays of 20, 30, 50, 50 or 100 contiguous amino acids drawn from anywhere within the 368-amino acid sequence SEQ ID NO:2. Claims 111-115 are rejected for lack of an adequate written description because the specification fails to exemplify or describe the detection, isolation or preparation of members of these distantly-related genera of divergent polypeptides. These rejected claims reach a myriad of generic DNA fragmentation factor polypeptides that differ substantially from the amino acid sequence of SEQ ID NO:2, yet neither the claims nor the specification describe where the differences occur or what such differences might be, nor how to distinguish a divergent, generic, human DFF40 DNA fragmentation factor amino acid sequence from a non-human DFF40 DNA fragmentation factor amino acid sequence. The requirement of claim 115 that a divergent DFF40 DNA fragmentation factor preserve an unspecified array of 100 contiguous amino acids of SEQ ID NO:2 somewhere within its otherwise unknown amino acid sequence does not prevent other, flanking, amino acid regions from diverging substantially from the disclosed sequence, thus the artisan cannot identify other, divergent, DFF40 amino acid sequences, human or otherwise on the basis of the instant disclosure. "While one does not need to have carried out one's invention

before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of human DFF40 polypeptides diverging at all but 20, 30, 50, 100, or more, amino acid sequence positions from the sequence of SEQ ID NO:2.

In addressing the issue of whether the disclosure of the molecular structure of a single species of polypeptide can adequately describe the molecular structures of other species of polypeptides defined mainly by functional similarity, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, DFF40 DNA fragmentation factors. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the generic DFF40 DNA fragmentation factor polypeptides of claims 111-115.

Claims 111-115 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for the preparation of functioning DFF40 DNA fragmentation

factors having amino acid sequences that diverge from the amino acid sequence of SEQ ID NO:2 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 94%, or even 70%, of the 338 amino acid positions within SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 111-115 contemplate, see pages 17-18 of the specification, the preparation of large genera of polypeptides comprising arbitrary assignments of any or all of amino acid substitutions, additions or deletions outside of unspecified, contiguous, arrays of from 20 to 100 amino acids abstracted from the human DFF40 DNA fragmentation factor amino acid sequence set forth in SEQ ID NO:2. The most permissive explicit requirement, a 20-amino acid array of claim 112, would conserve only 6% of the 338-amino acid sequence of SEQ ID NO:2 and the most permissive requirement of claim 115 that a DFF40 amino acid sequence preserve an array of 100 contiguous amino acids taken from somewhere within the overall sequence of SEQ ID NO:2 permits the other, flanking, 238 amino acid positions therein – constituting 70% of the DFF40 amino acid sequence – to diverge completely from the amino acid sequence of SEQ ID NO:2. The suggestion at page 17 of the specification a signal peptide be deleted is inappropriate for a polypeptide such as the DFF40 fragmentation factor which functions inside cells, and the specification's proposals, page 22, that domains of DFF40, DFF45 and ICAD polypeptides of different species of animals be "switched" to form chimeric polypeptides cannot support the claim limitation "human" and provides no guidance as to what domains may be spliced, nor where the splicing should occur, in order to conserve the capacity of variant DFF40 DNA fragmentation factors to be properly folded by a human, or other, DFF45 chaperonin, a semi-regulatory step within the cell that sustains DFF40 DNA fragmentation activity.

Claims 111-115 are rejected for lack of enablement under the first paragraph of the statute because the specification cannot support the breadth of the proposed modifications contemplating the preparation of polypeptides having amino acid modifications of the

amino acid sequence of SEQ ID NO:2 at 238 or more positions therein – where the modifications include amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in regions that flank an array of 100 in claim 115, 50 in claim 114, 30 in claim 113, 20 in claim 112, or fewer in claim 111, contiguous amino acids at unspecified locations within SEQ ID NO:2 – yet provide a DNA fragmentation factor that will form a complex with the DFF45 factor and function within a cell. Indeed, neither Applicant's specification nor the prior art made of record herewith can identify, taken together, such great numbers of positions in the amino acid sequence of SEQ ID NO:2 that can be altered, nor teach the nature such alterations, which will permit the divergent polypeptide to form a complex with the DFF45 factor and to also support DNA fragmentation activity. Mere sequence perturbation cannot enable the design and preparation of a myriad of divergent DFF40 fragmentation factors and provide the public with a useful DNA fragmentation factors retaining its native function.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree

of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace another, specific, variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands, supra*, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for preparing altered human DFF40 DNA fragmentation factors diverging at 238 or more amino acid positions from the amino acid sequence set forth in SEQ ID NO:2 embraced by claims 111-115,

b) the specification lacks working examples of the preparation of an altered human DFF40 DNA fragmentation factors diverging at even one amino acid position from the amino acid sequence set forth in SEQ ID NO:2,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of DFF40 DNA fragmentation factors capable of forming a complex with a DFF45 polypeptide and supporting nuclear DNA fragmentation activity have had any native amino acid sequence positions specifically identified for concurrent modification.

Thus the scope of subject matter embraced by the recitations, "wherein the DNA fragmentation factor comprises 20[or 30, or 50, or 100] contiguous amino acids of SEQ ID NO:2", is unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 111-116 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent claim 111 is indefinite in reciting, "polypeptide **encoding** a human DFF40 fragmentation factor", because one polypeptide cannot encode another and because Applicant's telephone conversations following Applicant's receipt of Paper No. 9 indicate that Applicant had desired to claim polypeptides. Polypeptides cannot be replicated, transcribed, or translated on the basis of any code inherent in their structure and are instead recognized in the relevant art of molecular biology to be products that are encoded by nucleic acids sequences. Claims 112-116 are subject to this rejection because they depend from claim 111 but do not clarify its ambiguous description. Amending claim 111 to delete the term "encoding" and to replace it with, e.g., "comprising", will overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 111 and 112 are rejected under 35 U.S.C. §102(a) as being anticipated by Enari et al., 01 January 1998, **Nature**, Vol. 391, No. 6662, pages 43-40, made of record with Applicant's Information Disclosure Statement.

Published over four months before the April 16, 1998, filing date of Applicant's priority application serial No. 09/061,702, Enari et al. disclose, see Figure 5d at page 47, the amino acid sequence of a CAD, a Caspase-Activated DNA fragmentation factor, that binds with a counterpart chaperonin, ICAD, homologous the human ICAD which is the human DFF45 polypeptide disclosed herein. The CAD of Enari et al. has the same

function as the DFF40 having the amino acid sequence of SEQ ID NO:2 herein, meeting the inherent functional limitations of claims 111 and 112 and this CAD of Enari et al. comprises an amino acid sequence identical to the 22-amino acid array from position 246 through position 277, inclusive, of SEQ ID NO:2, thus meets the structural limitations of claim 112 as well as claim 111 from which claim 112 depends. Because the source designation "human" in claim 111 cannot be given any weight in construction of claims 111-115 drawn to variant DFF40 polypeptides in view of the discussion at page 17 of Applicant's specification, the disclosure of Enari et al. anticipates claims 111 and 112.

Allowable Subject Matter

While subject to the rejections above under the first and second paragraphs of 35 U.S.C. §112, claims 113-115 are allowable over the prior art of record herein because no prior art of record discloses or suggests the amino acid sequence of a polypeptide that meets structural limitations of the claims. Claim 116 is subject only to the rejection above under the second paragraph of 35 U.S.C. §112 and is likewise free of the prior art of record, thus amending claim 116 in independent form clearly describing a human DFF40 polypeptide comprising the amino acid sequence of SEQ ID NO:2 would be allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 703.308.3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
September 8, 2003

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